REMARKS

A. Summary of the Invention

Broadly, the present invention concerns a reagent kit for detecting the presence or absence of one or more specific nucleotides at a predetermined target position in a target nucleic-acid polymer.

The reagent kit includes a detection primer comprising a detection-primer nucleotide sequence having a primer-extension-initiation 3'-end nucleotide which constitutes a 3' terminal end of the detection primer. The detection-primer nucleotide sequence is complementary to a primer-hybridizing nucleotide sequence of the target nucleic-acid polymer with a nucleotide in the target nucleic-acid polymer complementary to the primer-extension-initiation 3'-end nucleotide of the detection-primer nucleotide sequence defining a primer-end complement nucleotide. The primer-hybridizing nucleotide sequence of the target nucleic-acid polymer extends towards the 3' end of the target polymer from the primer-end complement nucleotide. The primer-end complement nucleotide is located in the target polymer at a position 3'-ward of the predetermined target position. The position of the primer-end complement nucleotide is subject to a constraint that no nucleotide of the same type as the one or more specific nucleotides to be detected be located in the target polymer in any position between the position of the primer-end complement nucleotide and the predetermined target position.

The reagent kit of the invention further includes an enzymatic polymerizing agent.

The reagent kit of the invention also includes a plurality of nucleoside triphosphates. In a first aspect, the plurality of nucleoside triphosphates includes at least one deoxynucleotide and at least two different chain-terminating nucleotide analogues. At least one deoxynucleotide in such first aspect comprises a detectable label or an attachment moiety capable of binding a detectable label. In a second aspect, the plurality of nucleoside triphosphates includes at least one

deoxynucleotide and at least one chain-terminating nucleotide analogue. At least one chain-terminating nucleotide analogue in such second aspect comprises a detectable label or an attachment moiety capable of binding a detectable label. Each deoxynucleotide of the nucleoside triphosphates is complementary to a nucleotide which differs from any nucleotide to which a chain-terminating nucleotide analogue of the nucleoside triphosphates is complementary.

In use, the detection primer of the reagent kit of the invention can hybridize to the target nucleic-acid polymer at the primer-hybridizing nucleotide sequence and form a detection-primer extension product by an enzyme-catalyzed primer-extension reaction to permit the presence or absence of a specific nucleotide at the predetermined target position to be detected by detecting the presence or absence of a corresponding detectable label in association with the detection-primer extension product.

B. Summary of the Outstanding Office Action

In the outstanding Office Action, claims 97 through 116 inclusive of the application were rejected under 35 U.S.C. § 112, first paragraph, with the assertion that certain features recited in the claims were not described in the specification of the application as originally filed.

Specifically, it was asserted in the Office Action of 3 February 2003 that the expression "detecting the presence or absence of one or more specific nucleotides at a predetermined position" included in claims 97 through 116 inclusive directly or by reference was not supported in the specification of the application as originally filed.

With respect to claims 107 through 116 inclusive, which call for an admixture containing at least one deoxynucleotide and at least one labeled chain-terminating nucleotide analogue, it was asserted further in the outstanding Office Action that the expression "each deoxynucleotide of the admixture of nucleoside triphosphates being complimentary to a nucleotide which differs

from any nucleotide to which a chain-terminating nucleotide analogue of the admixture is complementary" was not supported in the original specification.

Claims 97 through 106 inclusive were rejected in the outstanding Office Action under 35 U.S.C. § 103 as unpatentable over published international PCT patent application WO 98/09282 to Holmes *et al.* ("the Holmes *et al.* '282 published PCT application"). It was asserted in the Office Action that the Holmes *et al.* published application disclosed methods for sequencing DNA which required the use of a primer, a polymerase, and an admixture comprising labeled deoxynucleotides and "at least two chain-terminating nucleotide analogues." It was asserted that the claims of the subject application did not require that each of the at least two chain-terminating nucleotides be different from one another.

It was further asserted in the outstanding Office Action that the Holmes *et al.* '282 published PCT application disclosed amplifying a target nucleic acid prior to sequencing wherein the amplification involved the use of a pair of primers with one other primers labeled with an attachment moiety. It was asserted that the Holmes *et al.* published application disclosed labeling nucleotides with radioactive isotopes or fluorescent moieties and exemplified the use of primers of 18 nucleotides. It was conceded that the Holmes *et al.* '282 published PCT application did not disclose packaging reagents required to practice the sequencing method in a kit. It was asserted, however, that reagent kits for performing diagnostic methods were conventional in the field of molecular biology at the time the invention of the subject application was made. It was asserted that it would have been *prima facia* obvious to one of ordinary skill in the art at the time the invention was made to have packaged the primer, polymerizing agent, and admixture of dideoxynucleotides and labeled nucleotides in a kit for assertedly expected benefits of convenience and cost effectiveness for practitioners in the art.

It was conceded in the Office Action of 3 February 2003 that the Holmes *et al.* '282 published PCT application did not disclose including an attachment moiety in a primer used for sequencing. It was asserted, however, that the Holmes *et al.* publication disclosed immobilizing

a strand of DNA to be sequenced and also disclosed the concept of labeling primers and of incorporating nucleotides having labels attached thereto which could assertedly serve as a means for immobilizing an extending nucleic acid. It was asserted that it would have been obvious to one of ordinary skill in the art at the time the invention was made to have modified the method of the Holmes *et al.* '282 published application so as to have included an attachment moiety in the primer for sequencing in order to have provided an alternative means for capturing and separating sequencing products.

C. Summary of the Present Amendments and Request for Reconsideration

Claim 97 has also been amended in paragraph (c) to call for -- at least two different chain-terminating nucleotide analogues.-- It is submitted that a person of ordinary skill in the art as of the time the subject application was filed would have understood the expression "at least two chain-terminating nucleotide analogues" used in original claim 97 to mean at least two different chain-terminating nucleotide analogues. The present amendment to claim 97 merely makes express what a person of ordinary skill in the art would have understood from the claim as originally presented. It is submitted therefore that the scope of claim 97 has not been changed by the present amendment and that the amendment to the claim does not constitute new matter.

New claims 117 and 118 have been added in the present response to specify that the primer-end complement nucleotide be located in the target nucleic-acid polymer at a position spaced a plurality of nucleotides away from the predetermined target position. New claims 117 and 118 find support in the application as filed, for example, at page 19, lines 10 through 25 and in Figure 2. It is submitted that new claims 117 and 118 do not constitute new matter.

Reconsideration of the subject application as amended above in light of the comments below is respectfully requested.

D. The Rejections Under 35 U.S.C. § 112, First Paragraph

It is submitted that there is ample support for claims 97 through 116 inclusive in the specification of the application as originally filed.

With respect to the expression "detecting the presence or absence of one or more specific nucleotides at a predetermined position," the tables associated with Examples 1 and 2 set forth in the specification of the application as originally filed, for example, disclosed the detection of the presence or absence of specific nucleotides at a predetermined position.

With respect to the expression "each deoxynucleotide of the admixture of nucleoside triphosphates being complimentary to a nucleotide which differs from any nucleotide to which a chain-terminating nucleotide analogue of the admixture is complementary" recited in claim 107, support may be found, for example, at page 19, lines 10 through 25 of the original specification and in Figure 2 as originally filed.

For the reasons noted above, it is submitted that claims 97 through 116 inclusive are fully supported by the specification and drawings of the subject application as originally filed. The rejection of claims 97 through 116 inclusive under 35 U.S.C. § 112, first paragraph, in the Office Action of 3 February 2003 was therefore without justification and should be withdrawn.

E. The Rejection Under 35 U.S.C. § 103

The Holmes *et al.* '282 published PCT application disclosed Sanger-type sequencing carried out on target single-stranded DNA immobilized on a solid support. See page 5, lines 25 through 29 of the Holmes *et al.* published application. At page 11, line 35 through page 12, line 9 the Holmes *et al.* published application disclosed nucleotide mixes for use in extending primers annealed to immobilized target single-stranded DNA in sequencing procedures of the application. Each nucleotide mix contained a single ddNTP corresponding to one of the four bases A, C, G, or T together with three dNTPs corresponding to the three bases other than the

base of the single ddNTP of the mix. The Holmes *et al.* application neither disclosed nor suggested the use or two or more different chain-terminating nucleotide analogues in a primer extension reaction.

Independent claim 97 as amended is directed to a reagent kit which includes a detection primer of certain specified characteristics, an enzymatic polymerizing agent, and a plurality of nucleoside triphosphates including at least one deoxynucleotide and at least two different chain-terminating nucleotide analogues. At least one deoxynucleotide of the admixture comprises a detectable label or an attachment moiety capable of binding a detectable label. It is submitted that a person of ordinary skill in the art, as of the effective filing date of the subject application, would not have attempted to use a reagent kit as defined in claim 97 of the subject application for the Sanger sequencing method of the Holmes *et al.* '282 published PCT application.

For the reasons set forth above, it is submitted that the Holmes *et al.* '282 published PCT application would have neither disclosed nor suggested the subject matter of independent claim 97 to a person of ordinary skill in the art as of the effective filing date of the subject application.

Claims 98 through 106 inclusive of the application as amended are dependent claims which depend upon independent claim 97 and consequently incorporate the limitations of claim 97 by reference. The reasoning set forth above concerning distinctions between the Holmes *et al.* '282 published PCT application and claim 97 therefore applies with equal force with respect to dependent claims 98 through 106 inclusive.

For the reasons set forth above, it is submitted that the rejection of claims 97 through 106 inclusive 35 U.S.C. § 103 as unpatentable over the Holmes *et al.* '282 published PCT application was unwarranted and should be withdrawn.

F. Conclusion

For the reasons set forth above, it is submitted that the claims of the subject application as amended fully meet the standards of 35 U.S.C. § 112, first paragraph, and are patentable over the art of record considered alone or in any combination. Early allowance of the application is therefore earnestly solicited.

Respectfully submitted,

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